REMARKS

The Office Action mailed June 6, 2006 has been received and reviewed. Claims 1 through 30 are currently pending in the application. Claims 1, 5, and 12 have been amended herein. New claims 21 through 30 have been added herein. Basis for new claims 21 through 30 can be found throughout the specification and more particularly at ¶¶ 28 and 35-45 and in original claims 1-10 and 12-17. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-10 and 12-17 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement. Specifically, it was thought that "the specification fails to describe any other representative species *Lactococcus* thymidylate synthase gene(s) [other than those for *L. lactis*] by any identifying characteristics or properties other than the functionality of being *Lactococcus* thymidylate synthase gene(s)." Office Action mailed June 6, 2006, at page 4. Applicants respectfully submit that the claim amendments overcome the rejections and request withdrawal of same.

Although the applicants do not agree that the application does not comply with the written description requirement, to expedite prosecution, claims 1, 5, and 12 have been amended herein. Specifically, claims 1, 5, and 12 have been amended to recite "wherein said thymidylate synthase gene is selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5." Basis for the amendments can be found throughout the specification and more specifically at ¶¶ 28, and 35-45. As claims 1, 5, and 12, as amended, specifically recite SEQ ID NO: 3 or SEQ ID NO: 5, applicants respectfully submit that *Lactococcus* species are adequately described by identifying characteristics other than the functionality of being *Lactococcus* thymidylate synthase gene(s). Consequently, applicants respectfully submit that the rejections of claims 1, 5, and 12 under 35 U.S.C. § 112, first paragraph, for lack of written description have been overcome. As such, applicants respectfully request withdrawal of the rejections of claims 1, 5, and 12 for lack of written description and reconsideration of same.

Furthermore, applicants respectfully submit that claims 2-4, 6-10, and 13-17 are allowable at least as depending, directly or indirectly, from allowable independent claims 1, 5, and 12 respectively. Consequently, applicants respectfully request the withdrawal of the rejections of claims 2-4, 6-10, and 13-17 under 35 U.S.C. § 112, first paragraph, for lack of written description and reconsideration of same.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-10 and 12-17 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the enablement requirement. Specifically, it was thought that "the specification, while being enabling for a *Lactococcus* strain comprising a disrupted thymidylate synthase gene, said gene comprising SEQ ID NOs: 3 and 5, does not reasonably provide enablement for a *Lactococcus* strain comprising a disrupted thymidylate synthase gene having and undefined percent identity to SEQ ID NOs: 3 and 5." Office Action mailed June 6, 2006, at page 5. Applicants respectfully submit that the claim amendments overcome the rejections and request withdrawal of same.

Although the applicants do not agree that the application does not comply with the enablement requirement, to expedite prosecution, claims 1, 5, and 12 have been amended herein. Specifically, claims 1, 5, and 12 have been amended to recite "wherein said thymidylate synthase gene is selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5." As claims 1, 5, and 12 specifically recite SEQ ID NO: 3 or SEQ ID NO: 5, applicants respectfully submit that these claims are adequately enabled and respectfully agree with the Examiner that the specification is enabling for a *Lactococcus* strain comprising a disrupted thymidylate synthase gene, said gene comprising SEQ ID NOs: 3 and 5. Consequently, applicants respectfully submit that the rejections of claims 1, 5, and 12 under 35 U.S.C. § 112, first paragraph, for lack of enablement have been overcome. As such, applicants respectfully request withdrawal of the rejections of claims 1, 5, and 12 for lack of enablement and reconsideration of same.

Furthermore, applicants respectfully submit that claims 2-4, 6-10, and 13-17 are allowable at least as depending, directly or indirectly, from allowable independent claims 1, 5, and 12 respectively. Consequently, applicants respectfully request the withdrawal of the

rejections of claims 2-4, 6-10, and 13-17 under 35 U.S.C. § 112, first paragraph, for lack of enablement and reconsideration of same.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 5-10 and 12-17 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to point out and distinctly claim the subject matter which the applicants regard as the invention. Specifically, it was thought that claims 5 and 12 and the claims dependent therefrom "are confusing because the connection between a defective thymidylate synthase gene and a transforming plasmid is unclear as recited." Office Action mailed June 6, 2006, at page 7.

Although the applicants do not agree that claims 5 and 12 are confusing, to expedite prosecution, claims 5, and 12 have been amended herein. Specifically, claims 5 and 12 have been amended to recite "wherein said transforming plasmid does not comprise an intact thymidylate synthase gene." As such, the applicants respectfully submit that the relation between the thymidylate synthase gene and the transforming plasmid is clear. Consequently, applicants respectfully submit that the rejections of claims 5, and 12 under 35 U.S.C. § 112, second paragraph, have been overcome. As such, applicants respectfully request withdrawal of the rejections of claims 5, and 12 for indefiniteness and reconsideration of same.

Furthermore, applicants respectfully submit that claims 6-10 and 13-17 are allowable at least as depending, directly or indirectly, from allowable independent claims 5 and 12 respectively. Consequently, applicants respectfully request the withdrawal of the rejections of claims 6-10 and 13-17 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

Claims 5-10 and 12-17 stand further rejected under 35 U.S.C. § 112, second paragraph, as it was thought that claims 5 and 12 and the claims dependent therefrom are confusing as "claims 5 and 12 recite 'said transforming plasmid not having an intact thymidylate synthase gene' [and that] such a definition of the plasmid is confusing as defines it by what said plasmid is not instead of defining what it is." Office Action mailed June 6, 2006, at page 7. Applicants respectfully traverse the rejection as hereinafter set forth.

"The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation." M.P.E.P. §2173.05(i). As such applicants respectfully submit that claims 5 and 12 cannot be confusing for reciting what the plasmid is not instead of defining what it is. Consequently, applicants respectfully request withdrawal of the rejections of claims 5, and 12 for idefiniteness and reconsideration of same.

Furthermore, applicants respectfully submit that claims 6-10 and 13-17 are allowable at least as depending, directly or indirectly, from allowable independent claims 5 and 12 respectively. Consequently, applicants respectfully request the withdrawal of the rejections of claims 6-10 and 13-17 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-10 and 12-17 stand rejected under 35 U.S.C. § 103(a) as assertedly being obvious over Steidler *et al.* (Treatment of Murine Colitis by *Lactococcus lactis* Secreting Interleukin-10, *Science*, August 25, 2000, pp. 135-55, Vol. 27) (hereinafter "Steidler") in view of Taylor *et al.* (Molecular Characterization of the Cell Cycle-regulated Thymidylate Synthase Gene of *Saccharomyces cerevisiae*, *The Journal of Biological Chemistry*, April 15, 1987, pp. 5298-307, Vol. 262, No. 11) (hereinafter "Taylor"). Specifically it was thought that Steidler teaches a transformed *L. lactis* strain which secretes active murine IL-10 that is used to treat murine colitis. Office Action mailed June 6, 2006, at page 7. It was further thought that Taylor teaches the disruption of the thymidylate synthase gene in *S. cerevisiae* through the insertion of a 2.2 kb fragment of the LEU2 gene. *Id.* Additionally, it was thought that Taylor teaches that thymidylate synthase genes from various organisms show similar properties on the functional level. *Id.* at page 8. Applicants respectfully traverse the rejection as hereinafter set forth.

In order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 706.02(j). Applicants respectfully assert that the combination of Steidler and Taylor does not teach each and every element of claims 1, 5, and 12 as amended. Specifically, claims 1, 5, and 12, as amended, direct "wherein said thymidylate synthase gene is selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5." Applicants respectfully assert that the

combination of Steidler and Taylor does not teach that the thymidylate synthase gene is selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5. As such, applicants respectfully submit that claims 1, 5, and 12, as amended, cannot be obvious over Steidler in view of Taylor. Further, as claims 2-4, 6-10, and 12-17 depend directly and indirectly from claims 1, 5, and 12, respectively, applicants respectfully assert that claims 2-4, 6-10, and 12-17 are at least not obvious as depending, directly or indirectly, from a non-obvious base claim. Consequently, applicants respectfully request the withdrawal of the rejections of claims 1-10 and 12-17 under 35 U.S.C. § 103(a) over Steidler in view of Taylor and reconsideration of same.

Further, Steidler teaches away from the combination of Steider and Taylor to produce the claimed invention. The Examiner asserts, at page 8 of the Office Action mailed June 6, 2006, that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce an *L. lactis* strain which comprises a disrupted thymidylate synthase. This would allow one to use said strain for the delivery of a drug (molecule of interest) to a patient without contaminating the outside environment where thymidine/thymine is not present in amounts sufficient for said strain to survive." Applicants respectfully submit, contrary to the Examiner's assertion, that Steidler teaches that a functional thymidylate synthase is not required for survival. Steidler at page 5302, last paragraph, through 5303, first paragraph. As such, one of ordinary skill in the art would not combine the teachings of Steidler and Tayler to create a *Lactococcus* strain for the delivery of a drug (molecule of interest) to a patient without contaminating the outside environment. Therefore, as Steidler teaches that a *Lactococcus* strain having a defective thymidylate synthase would have no purpose, applicants respectfully submit that the Examiner has provided no motivation to combine the references.

In addition, contrary to the Examiner's assertion, there is no reasonable expectation of success. Taylor describes the disruption of the TMP1 gene in the yeast *S. cerevisiae*, by homologous recombination. However, homologous recombination is relatively frequent in this yeast, whereas it is rare in *Lactococcus*. Moreover, as genomic integration by homologous recombination is a rare event, even in yeast, a very efficient transformation system is needed. Therefore, although gene inactivation by homologous recombination is a standard technique in yeast, application in other organisms, especially in bacteria like *Lactococcus* sp., where the

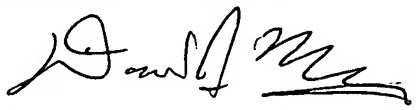
transformation efficiency is rather low, is far from evident. Examples of successful gene inactivation by homologous recombination in *Lactococcus* are rare, and the skilled person would certainly not design such an experiment with a reasonable expectation of success.

This is supporteed by Ross *et al.* (Thymidylate Synthase Gene from *Lactococcus lactis* as a Genentic Marker: an alternative to Antibiotic Resistance Genes, *Applied and Environmental Microbiology*, July 1990, pp. 2164-69, Vol. 56, No. 7), among others. Ross *et al.* describe the cloning of the *Lactococcus lactis* gene and its use as an alternative for an antibiotic resistance gene. Although they could have tested this gene as marker in the *Lactococcus lactis* thyA mutant, and although they used *E. coli* and *Rhizobium meliloti* thyA mutants as recipient strains, the gene was tested in wild type *L. lactis*, reflecting the difficulty in constructing such a mutant. The authors constructed the *R. meliloti* thyA mutant, but not the more scientifically and conceptually straightforward *L. lactis* mutant. Although the sequence of the thyA gene was available, although mutants have been described in other species, and although the combination *L. lactis* thyA mutant and thyA gene would have been an ideal transformation system in an economically important species, nobody succeeded in creating this mutant until this application, either by classical mutagenesis, or by gene disruption. Given this reasoning, applicants submit that the present claims are not obvious under 35 U.S.C. § 103(a) over Steidler in view of Taylor.

In view of the foregoing remarks and amendments, applicants respectfully submit that the rejections of claims 1-10 and 12-17 under 35 U.S.C. § 103(a) are improper. Consequently applicants respectfully request the withdrawal of the rejections of claims 1-10 and 12-17 under 35 U.S.C. § 103(a) and reconsideration of same.

If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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